Heterocycles Derived from the Condensation of 1,3-Propanediamine with Phthalic Acid Derivatives

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The condensation of phthalic anhydride with 1,3-propanediamine afforded *N*-(*o*-carboxybenzoyl)-1,3-propanediamine (I) which by intravolecular cyclization was transformed into 2,3,4,6-b-tetrahydropyrimido[2,1-*a*]isoindol-6-one (II) rather than the benzodiazonine (III). An intermediate in the condensation is proposed. The reaction of 1,3-propanediamine with dimethyl phthalate also did not afford III, but rather a more complex product, dibenzo[*c*,*l*]-1,6,10,15-tetraazacyclooctadecane-5,11,16,22-tetraone (IX). Reaction of 1,3-propanediamine with phthaloyl chloride gave 6,13-propanodibenz[*c*,*h*]-1,6-diazecine-5,7,12,14-tetrone (XII). Spectroscopic data of the heterocycles obtained and chemical properties of II are given.

As part of our interest in the chemistry and pharmacological activity of medium-sized ring compounds we explored the possibility of preparing some 2,6-benzodiazonines. The reaction of 1,2 or 1,3-diamines with aldehydes, ketones or carboxylic acid derivatives has found general application in the preparation of heterocyclic systems, but this reaction of bifunctional molecules could, however, result in products other than the desired one (1,2,3) or in a mixture of products.

At the time our work was initiated, no systematic study of the type of product formed when 1,3-propanediamine is condensed with phthalic anhydride or derivatives of phthalic acid had been carried out. The present paper reports our findings on them and discusses the steps of the reaction and chemical and spectroscopic properties of the heterocycles obtained.

The reaction of equimolecular amounts of 1,3-propanediamine with phthalic anhydride in ethanol solution gave a water soluble compound. This solubility and its analytical and spectroscopic properties are in agreement with the structure I (Scheme I). The infrared spectra showed broad absorption at 3225-2940 cm^{-1} and a strong band at 1623 cm^{-1} typical of a NH_3^+ and CO_2^- grouping, respectively. Heating I above its melting point gave a compound consistent with the tricyclic structure II which is related to an isoindolone rather than the benzodiazonine III as expected.

TABLE I

Compound	Infrared Spectrum (cm^{-1}). NH amine	NH amide	OH	C=O amide	C=O acid	C=N	Ultraviolet Spectrum (a) λ max. mμ	lg E
I	3330	2940	3100	1630	1520	----	242	4.48
II	----	----	----	1720	----	1660	222	4.28
V	3470	----	3030	----	1640	1560	227	4.23
VI	3300	3100	----	1740	----	1630	231	4.26
VII	----	----	3280	----	----	1620	236	4.34
VIII	----	----	----	1770	----	1690	224	4.21
IX	----	3330	----	1630	----	----	---	---
XII	----	----	----	1785 (b) 1770	----	----	227	4.29

(a) Concentration: 1 mg./100 ml. (b) Diacylimide structural unit.

TABLE II

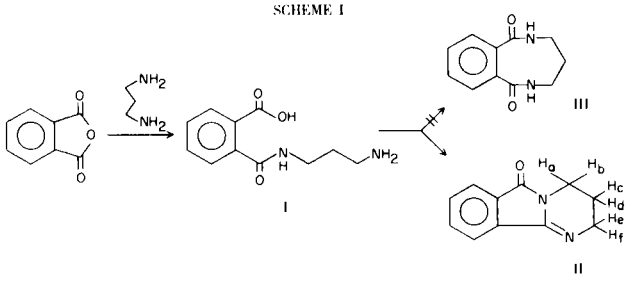
Nuclear Magnetic Resonance Data (a) (δ, ppm)

Compound	H_b	OH	Aliphatic Protons	Aromatic Protons
II (b)	2.63	---	1.93 (2H,Q,CCH_2C); 3.74 (3H,T,CCH_2N and CH_a)	7.63 (4H,M)
VII (c)	4.43	1.23	1.80 (2H,M,CCH_2C); 3.43 (3H,T,CCH_2N and CH_a) 5.95 (1H,S,ArCH)	7.28 (4H,M)
V (d)	---	---	1.91 (2H,M,CCH_2C); 3.33 (4H,T,CH_2N)	7.46 (4H,Q)
I (d)	---	---	1.70 (2H,M,CCH_2C); 2.84 (4H,M,$CONCH_2CH_2$)	4.10 (4H,M)

(a) The aliphatic protons were present as a series of overlapping multiplets. The value in the table refers to the center of these overlapping multiplets. J: 6 cps in all compounds. (b) Solvent: deuteriochloroform. (c) Solvent: deuteriochloroform; the presence of the OH group was confirmed by deuterium oxide exchange at room temperature. (d) Solvent deuterium oxide.

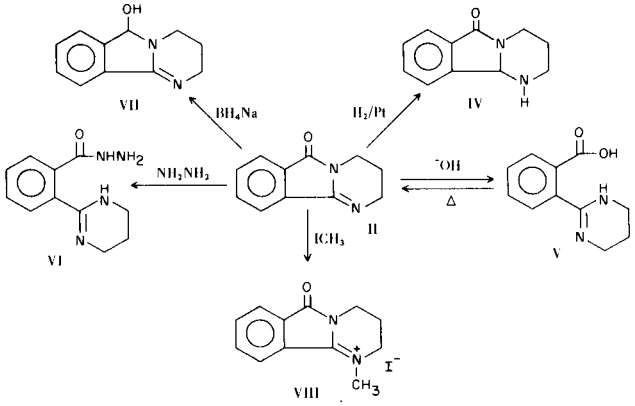
The structure II was determined by the ultraviolet absorption of λ max 223 mu, similar to that of known substituted isiondolones (4). The structure assigned is supported by the infrared spectra which displays a typical five-membered ring lactam carbonyl band and imine absorption band (5) (Table I). Finally the previously described compound IV (2) was obtained from II by mild catalytic hydrogenation. The absence of absorption bands in the NH region rules out the possibility of a structure with a CONH-function such as III. Compound II shows a singlet in the nmr spectra (Table II) assigned to H_b. The lack of geminal coupling between H_a and H_b is consistent with the fact that the conformational orientation is not readily predicted from inspection of simple molecular models. The orientation of the CH_aH_b group in this compound is undoubtedly one where the H_b proton lies in the plane of the carbonyl group (6,7). The methylene protons CH_cH_d are magnetically equivalent because this group is flanked by two methylene groups, but owing to the lack of geminal coupling between H_a and H_b, give rise to a quartet. A fifth line can be observed that enlarges the quartet, owing possibly to the mutual coupling of protons having equal chemical shift (H_a, H_e, and H_f).

SCHEME I

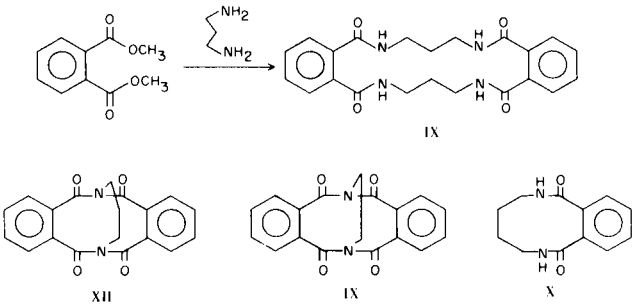


Compound II is a stable basic substance that forms a non hygroscopic water soluble hydrochloride. Refluxing in 50% hydrochloric acid caused no hydrolysis, but with concentrated acid total hydrolysis produced phthalic acid.

SCHEME II



SCHEME III



Mild alkaline hydrolysis of II gave a product with properties typical of an aminoacid; elemental analysis, infrared, ultraviolet (Table I) and nmr spectra (Table II) support the structure V (Scheme II); when this compound was heated at 210°, it lost water easily and regenerates compound II. Therefore the pyrimidine V is suggested as the intermediate step not isolated in the synthesis of II from I.

The degradation of II was also performed with hydrazine, which afforded VI, the structure of which was confirmed by ir and ultraviolet spectra.

Treatment of II with sodium borohydride in refluxing ethanol gave the corresponding hydroxy derivative VII.

The presence of only one deuterium oxide exchangeable proton in the nuclear magnetic resonance spectra and OH and C=N groupings in the ir spectra supported the assigned structure.

Reaction of II with methyl iodide gave the corresponding ternary iminium iodide VIII. This compound was inert to nucleophilic reagents as potassium cyanide, Grignard reagent and sodium hydroxide. Attempts to reduce II in order to obtain the basic saturated ring by means of lithium aluminum hydride failed to yield identifiable products.

In order to determine the relation between structures III and V, the reaction of 1,3-propanediamine with dimethyl phthalate was carried out. In the presence of catalytic amounts of sodium isopropoxide in isopropyl alcohol a compound which had a high melting point and was insoluble even in the most polar solvents was obtained. Elemental analysis and infrared spectra (Table I) are in agreement with the benzodiazonine structure III, but the properties above mentioned prompted us to consider a much larger molecule. Its molecular weight determined by mass spectra (see Experimental) is consistent with the dimeric structure IX (Scheme III).

The benzodiazocine X was described by Steter (8) as the product of the reaction between phthaloyl chloride with ethylenediamine although in a later investigation, Wolfe and Hassan (9) determined that the actual structure of the compound is the bridged dibenzodiazecine XI. In our hands a similar reaction with 1,3-propanediamine furnished 6,13-propanedibenzo[*c*,*h*]-1,6-diazecine-5,7,12,14-tetraone (XII). As XI, the ir spectra of XII shows strong carbonyl absorption band at 1785 and 1709 cm^{-1}., indicative of a diacylamide unit.

EXPERIMENTAL

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra (potassium bromide) were obtained on a Perkin-Elmer model 137 spectrophotometer. Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer model 350 spectrophotometer. Nmr spectra were recorded on a 60 Mc Perkin-Elmer R-12 spectrometer and chemical shifts are reported in parts per million (δ) down-field from the TMS reference. Mass spectra were recorded on a AEI M 59 mass spectrometer.

N-(*o*-Carboxybenzoyl)-1,3-propanediamine (I).

To a solution of phthalic anhydride (26 g., 0.175 mole) in 100 ml. of ethanol was added dropwise with stirring, 1,3-propanediamine (13.702 g., 0.184 mole); an exothermic reaction took place, the mixture was stirred for 45 minutes and allowed to cool, then the precipitate was collected and air-dried. No satisfactory recrystallization solvent could be found. Consequently, the solid was triturated thoroughly with dry chloroform and collected by filtration to give 37.44 g. (97%) of a microcrystalline white product, m.p. 195-197°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.4; H, 6.30; N, 12.61. Found: C, 59.6; H, 6.28; N, 12.64.

2,3,4,6b-Tetrahydropyrimido[2,1-*a*]isoindol-6-one (II).

Compound I (100 g., 0.450 mole) was heated in an oil bath with stirring at 210-220°. The evolution of water was rapid and complete in 1 hour. The temperature was then lowered, maintained at 100° and with vigorously stirring, 150 ml. of ligroin was added. The mixture was allowed to cool, the solid collected and air-dried to give 70 g. (83%) of crude product, m.p. 57-60°. A small sample was recrystallized twice from ligroin to give the analytical sample, white needles, m.p. 80-82°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.9; H, 5.37; N, 15.05. Found: C, 70.8; H, 5.42; N, 15.15.

1,2,3,4,6,10b-Hexahydropyrimido[2,1-*a*]isoindol-6-one (IV).

A stirred solution of 4 g. (0.021 mole) of II in 200 ml. of methanol with 0.4 g. of platinum oxide was hydrogenated at normal pressure and at room temperature for 3 hours. The catalyst was removed by filtration and the solution was evaporated to dryness and the resulting light solid was extracted by refluxing with petroleum ether (b.p. 80-100°). The solution was allowed to cool to give 3.08 g. (75%) of white needles. Recrystallization from benzene-cyclohexane gave the pure product, m.p. 125-127°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.38; N, 14.9. Found: C, 70.3; H, 6.35; N, 14.8.

2-(*o*-Carboxyphenyl)-1,4,5,6-tetrahydropyrimidine Hydrochloride (V).

A mixture of 3.72 g. (0.02 mole) of II, 2 ml. of 60% potassium hydroxide and 40 ml. of methanol was refluxed for 3 hours; the solvent was removed *in vacuo* and the solid residue was dissolved in 40 ml. of water and the solution adjusted to *p*H 5 with 50% hydrochloric acid. The water was then evaporated *in vacuo*, the residue was extracted with methanol (40 ml.), and the salts removed by filtration. Total evaporation of the methanol gave a white amorphous solid that was triturated with ether to give 3.9 g. (81%) of a very hygroscopic product. Recrystallization from isopropyl alcohol gave white prisms, m.p. 164-166°.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_2$: C, 54.8; H, 5.44; N, 11.7. Found: C, 54.8; H, 5.47; N, 11.5.

2,3,4,6b-Tetrahydropyrimido[2,1-*a*]isoindol-6-one (II) from (V).

Compound V (0.15 g., 0.62 mole) was heated in an open tube at 210° for 1 hour, the residue was crystallized from ligroin to give 0.10 g. (86%) of a product which was identical in all respects with an authentic sample of II.

2-(*o*-Carbohydrazidophenyl)-1,4,5,6-tetrahydropyrimidine (VI).

To a solution of II (1.86 g., 0.1 mole) in ethanol (25 ml.) was added 1.4 ml. of 98% hydrazine hydrate. The mixture was refluxed for 2 hours; the precipitate formed was washed with isopropyl alcohol to give 1.3 g. (60%) of crude product. This product was recrystallized three times from water-isopropyl alcohol to give a white microcrystalline solid, m.p. 233-234°.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.5; H, 6.42; N, 25.7. Found: C, 60.9; H, 6.04; N, 25.4.

2,3,4,6b-Tetrahydropyrimido[2,1-*a*]isoind-6-ol (VII).

To a stirred solution of II (3.0 g., 0.016 mole) in 100 ml. of ethanol was added sodium borohydride (2.5 g., 0.07 mole). The mixture was refluxed for 24 hours. The solution was then spin-evaporated *in vacuo* to dryness. To the solid residue was added 120 ml. of water and the mixture was stirred until total disolution

had occurred. This solution was extracted with methylene chloride by means of a liquid-liquid extractor (downward displacement type) for 24 hours. The solution was concentrated by distillation of solvent and then cyclohexane was added to give a white solid (0.75 g., 25%). Upon recrystallization from chloroform-cyclohexane, colorless needles, m.p. 173-174°, were obtained.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.38; N, 14.9. Found: C, 70.1; H, 6.40; N, 14.6.

2,3,4,10b-Tetrahydro-1 methylpyridinium[2,1-*a*]isoind-6*H*-one Iodide (VIII).

To a solution of 0.6 g. (3.2 mole) of II in 7 ml. of dry benzene was added methyl iodide (2.0 ml.). The resultant solution was refluxed for 20 minutes. The yellow solution was allowed to stand at room temperature for 2 days to give 0.52 g. (49%) of an amorphous yellow solid. A portion was recrystallized from dimethylformamide-benzene to give yellow prisms, which decomposed at 280° without melting.

Anal. Calcd. for $C_{12}H_{13}N_2OI$: C, 43.9; H, 3.96; N, 8.53. Found: C, 44.0; H, 3.93; N, 8.54.

Dibenzo[*c,l*]-1,6,10,15-tetraazacyclooctadecane-5,11,16,22-tetraone (IX).

Methyl phthalate (12.5 g., 0.064 mole) and 1,3-propanediamine (4.8 g., 0.064 mole) were added portionwise with stirring to a solution of sodium isopropoxide, prepared from 40 ml. of isopropyl alcohol and 0.15 g. of sodium. The mixture was refluxed for 16 hours and the precipitate was collected and washed with isopropyl alcohol to give 2.1 g. (8%) of a white microcrystalline solid, m.p. 274-275°. The solid was powdered and refluxed with pure dimethylformamide, then allowed to cool, and the solid collected by filtration, was analytically pure, m.p. 277-278°.

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.6; H, 5.88; N, 13.7. Found: C, 64.6; H, 5.91; N, 13.7. Mol wt (mass spectra): Calcd: 408. Found: 395.

6,13-Propanedibenzo[*c,h*]-1,6-diazecine-5,7,12,14-tetraone (XII).

Solutions of phthaloyl chloride (2.0 g., 0.01 mole) in dry benzene (200 ml.) and dry 1,3-propanediamine (1.48 g., 0.02 mole) in dry benzene (200 ml.) were prepared. A three-necked flask was fitted with a magnetic stirrer and a nitrogen inlet. The flask was fitted with precision dropping funnels and then charged, under nitrogen, with dry benzene (150 ml.). The two reactants were added to the flask at room temperature. Addition was complete in 3 hours. The reaction mixture was allowed to stand 48 hours, and a dense paste was removed by decantation. The solution was evaporated to dryness to yield 0.380 g. (6%) of a microcrystalline white solid. The product was recrystallized twice from benzene-cyclohexane to give an analytical sample, m.p. 127-129°.

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.3; H, 4.19; N, 8.38. Found: C, 68.5; H, 4.17; N, 8.36.

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